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To infinity … and beyond! Human spaceflight and life science

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The early writings of Jules Verne (*From the Earth to the Moon,* 1865; **Fig. 1**) and H. G. Wells (*First Men on the Moon*, 1901; **Fig. 2**) were the starting point of science fiction and the dream of space exploration. Verne proposed a "projectile bullet capsule" shot from a long cannon named Columbiad as a means for 3 explorers to achieve the escape velocity needed to leave Earth's gravity (1). Even in 1865 there were concerns about humans' ability to survive extreme velocities. Verne made crude calculations on the length of cannon needed for a human to survive a launch to the moon. Almost 100 yrs later, the United States used a very similarly shaped Apollo capsule named *Columbia* to take 3 astronauts—Armstrong, Collins, and Aldrin—to the moon and return to Earth.

Figure 1.

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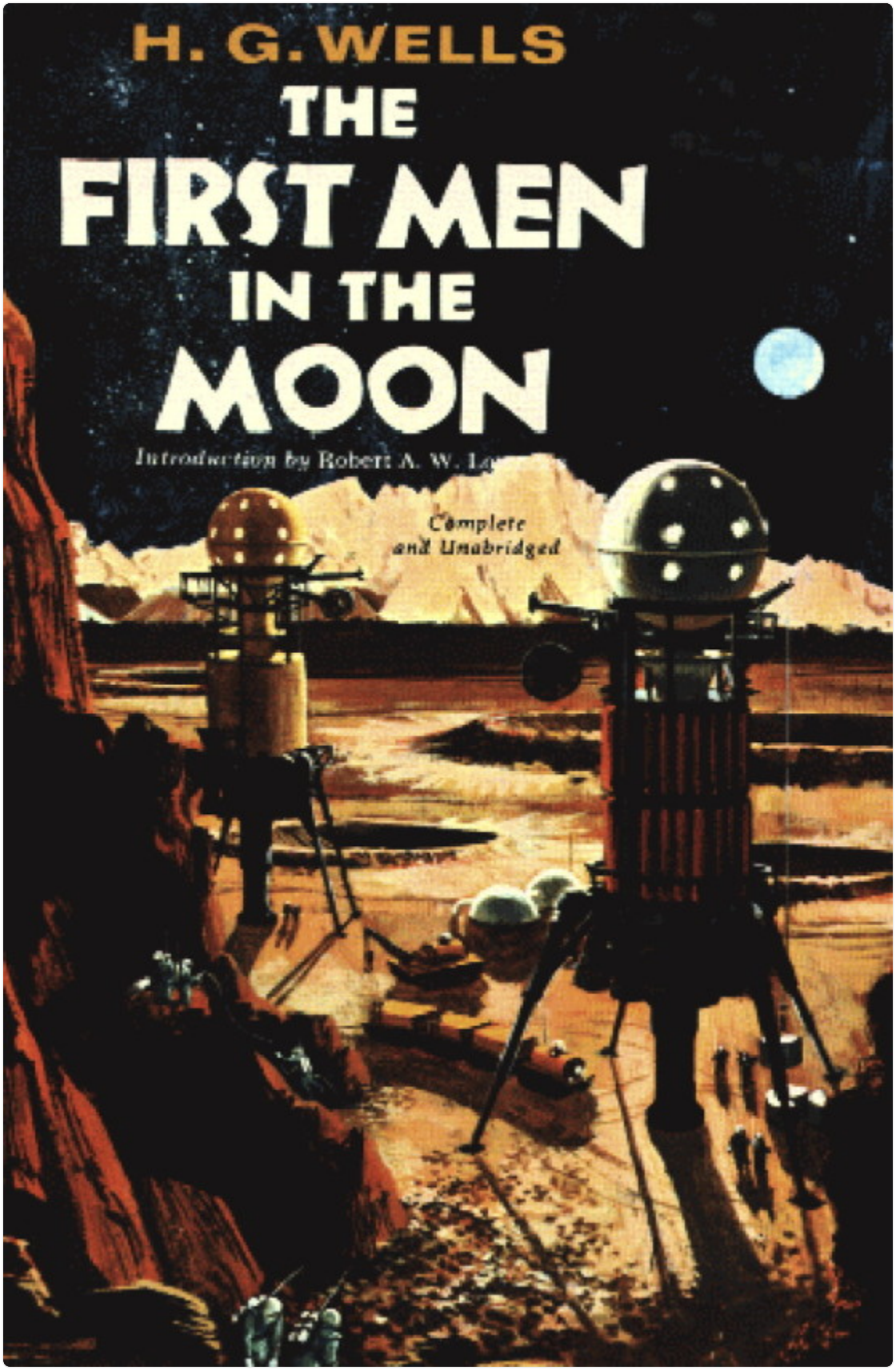
Jules Verne's “bullet capsule,” designed to take 3 explorers to the moon by being shot from a very long gun barrel. Illustration from the novel *From the Earth to the Moon* by Jules Verne; drawn by Henri de Montaut (1868). Image courtesy private collector.

Figure 2.


H. G. WELLS
THE
FIRST MEN
IN THE
MOON
Introduction by Robert A. W. Lo
Complete
and Unabridged

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Paperback cover illustration for *First Men in the Moon* by H. G. Wells, first published in 1901. Image courtesy Airmant Publishing Co., Inc.

The vision of spaceflight began with science fiction literature, which was followed decades later by the science, engineering and other technological achievements that made it a reality. It took the momentum of war to further advance technology to a point where space travel was possible. After World War II, the United States and the USSR repurposed the spoils of war, transforming the once terrorizing German V-2 rocket program into new space programs. Some vehicles are specifically designed for suborbital (ballistic) flight; examples include crewed vehicles, such as the X-15 rocket plane, sounding rockets, and Virgin Galactic's *SpaceShipTwo*, and uncrewed rockets, such as intercontinental ballistic missiles (ICBMs).

The first spaceflight was ballistic and reached an altitude of 17 nautical miles (31.5 km) above the earth. Ballistic flights, by definition, do not go into orbit and have only brief periods of microgravity (10^{-3} to 10^{-6} *g*). During ballistic flights, spaceflight microgravity lasts from a few seconds or minutes to a few hours before returning to the planet. This type of flight only offers short opportunities for scientific query.

Orbital flights travel at ~17,500 nautical miles per hour (~32,400 km/h) around the planet and are on a different scale of experimental time since microgravity can last from days, weeks, and months to years. Orbital flights support a wide range of science investigations from signal transduction and gene expression to differentiation, physiology, and development. The height of the orbit around Earth depends on the spaceship: the shuttle orbited at ~160 nautical miles (~300 km), whereas the International Space Station (ISS) is in a near-circular orbit at ~192 nautical miles (~360 km). The U.S. military and the National Aeronautics and Space Administration (NASA) award astronaut flight medals to crew members that fly ≥50 nautical miles above the earth. With the exception of the X-15 rocket plane and early Mercury flyers, most astronauts accomplished their required altitude on orbital flights.

With the flight of the first human-made object into orbit on October 4, 1957, Sputnik 1 started the intense competition between the USSR and the United States, vying for the number-one spot in the Space Race. To determine whether animals could survive launch forces, both countries flew animals to test the sustainability of life during spaceflight and started the fields of gravitational and space biology. Nikita Khrushchev ordered the first orbital spaceflight of an animal after the successful flight of Sputnik 1. He wanted to have a spectacular launch on November 7, 1957, the 40th anniversary of the Bolshevik Revolution. In response to his request, Soviet planners and engineers came up with an orbital flight with a dog onboard. A stray, Laikia (**Fig. 3**), was picked to be the first dog in space because of her survival skills on the snowy streets of Moscow. Unfortunately, in the rush to make the deadline, there was no time to plan a sustainable environmental system or a reentry plan. Laikia, the first Earth being to orbit the planet, did not survive her

flight.

Figure 3.

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Laika, the first animal to orbit the earth (1957). Image courtesy author's photo collection.

Later spaceflights were used to study the effect of microgravity on living systems and the requirement of gravity for normal function of the body's systems. The Apollo missions were the first to show significant changes in multiple biological systems in spaceflight. These changes included vestibular disturbances, in-flight cardiac arrhythmia, reduced postflight orthostatic tolerance, postflight dehydration, and weight loss. Scientists also found a significant decrease in red blood cell mass (RBCM). Other major changes documented were the negative in-flight balance for nitrogen and a significant loss of calcium and bone (2–5).

These observations helped guide NASA scientists to plan more detailed physiological studies during the Skylab era (1973–1974; **Fig. 4**). During the Skylab missions, scientists conducted the first detailed metabolic and immune studies. When Skylab crew members were tested for osteoporosis in the os calcis (the largest bone of the heel), bone loss was only apparent on the longer Skylab missions (5).

Figure 4.

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Skylab 3 (1973–1974), the first NASA space station. Image courtesy NASA.

It was on the Skylab missions that the significant changes in the immune function were first studied in detail. Lymphocytes from the flight crew and the backup crew were tested for phytohemagglutinin (PHA)-stimulated growth preflight, on landing and then again 13 d later. There were no significant changes seen in immune response in the backup crew; however, the vast majority of the response of the T cell was lost in the flight crew on return to Earth. Immune function did not return until 13 d later (6). Skylab experiments also showed the benefits of vigorous exercise as a countermeasure to minimize cardiovascular deconditioning.

The Skylab 4 mission was the first to study the occurrence of visual light flashes that had first been noted on Apollo 11. One astronaut counted a total of 168 flashes over 2 sessions. It was thought that the flashes seen after dark adaptation were due to ionization energy loss as a particle traversed retinal cells (7). On my flight in 1991, we were told that there was a solar flare; after I closed my eyes that night, I remember watching brilliant flashes of light—I fell to sleep before my count got to 20.

In 1991, NASA flew the first dedicated medical mission, designated as Spacelab Life Sciences-1 (STS-40). The crew consisted of 7 members: 3 orbiter astronauts and 4 payload astronauts. The mission was designed to study the cause of the physiological changes that were previously observed during Apollo, Skylab, and the USSR programs. The physiological space adaptations discussed here are fluid shift (due to the lack of gravity pulling fluid the lower body) and space anemia (the loss of RBCM); space osteoporosis and loss of calcium; and immunosuppression in space.

FLUID SHIFT AND SPACE ANEMIA

During spaceflight, the volume in the lower limbs decreases by ∼10% due to a 1- to 2-L fluid shift from the legs to the upper body. The facial fullness and puffy appearance of the head and reduced volume in the lower limbs is referred to as “puffy face-bird leg” syndrome (8). Space studies of plasma volume showed a 22% decrease from the average plasma volume taken from preflight data. This loss of plasma volume occurred by d 2 of flight even though the crew was diligent in keeping a high state of hydration. On d 8 of flight, there was still a 12% decrease in plasma volume, and it took 6 d after landing for the crew's plasma volume to return to preflight levels. The reduction of plasma volume during spaceflight is most likely a result of the fluid shift that is sensed by the body and results in an increased diuresis (9). When plasma volume was reduced, there was a dramatic decrease in erythropoietin (EPO), a glycoprotein made in the renal cortex.

The study of the influence of spaceflight on the erythrokinetics in humans was found to be caused by the reduced plasma EPO that, in turn, affected various hormones, such as atrial natriuretic peptide (ANP). ANP was reduced by 20% from d 1 of flight, with the nadir of ∼60% on d 8 of flight (10–13). The levels of serum ANP did not return to normal until 6 d after landing. Serum EPO levels decreased ∼40% by d 2 of flight and remained depressed until the day after landing, at which time it rebounded almost 2-fold compared to the preflight baseline levels.

Alfrey *et al.* (11) found that RBC survival was reduced during spaceflight by apoptosis of RBCs due to insufficient sera levels of EPO during spaceflight. After this breakthrough finding from his space experiments, Alfrey continued studies of RBC regulation and has shown that red cell mass is decreased when the sera level of EPO is suppressed. This leads to the selective hemolysis of the youngest circulating RBCs, called neocytes. The process is now called neocytolysis and has been confirmed with a variety of physiological and pathophysiologic situations, including descent of high-altitude dwellers to sea level, the anemia in renal failure, and in a human model based on EPO administration and withdrawal (13–18).

SPACE OSTEOPOROSIS

Bone loss was also well documented on the Apollo and Skylab missions. Osteoporosis is currently one of the most serious health hazards of long-term spaceflight. There is continuous and progressive loss of calcium and weight-bearing bone (19) during exposure to microgravity. In an early review, it was shown that there is a loss of bone in both humans and animals after 1 wk to 237 d in microgravity (19). SLS-1 was the first opportunity to systematically measure parathyroid hormone (PTH) and calcium in serum samples from both male and female crew members during spaceflight. Arnaud and Cann (20) found a significant increase in serum-ionized calcium of ~30% by d 2 of flight. Ionized serum calcium measured on d 8 was still elevated by ~30%, measurements of PTH on the same days showed an ~50% decrease in intact PTH (iPTH) during the mission. Even 16 d after landing, neither calcium nor iPTH values returned to normal (20).

The loss of bone on the Apollo 14–16 missions was almost 2%, even though the spaceflights lasted only 9 to 12 d (5). Although the Apollo missions were short in duration, the Apollo astronauts spent much of their time strapped down in a small capsule and were relatively immobile. The first crewed Skylab mission (Skylab 2) was 28 d, but because of extensive crew activity, no significant bone loss was noted. However, when Skylab missions increased to 2 and 3 mo, a significant loss of bone was seen (5). On Skylab 3 (59 d) only the scientist pilot had significant bone loss; on Skylab 4 (84 d), both the scientist pilot and the pilot had high levels of bone loss, suggesting that the length of exposure to weightlessness was a causal factor in loss of bone homeostasis (5). The commanders had little to no change in bone density, most possibly due to the increased exercise required in their duties. The underlying cause of the bone loss is thought to be due to the loss of mechanical stress in microgravity and duration of flight (8, 21–23).

Vico *et al.* (24) have reported up to a 24% loss of distal tibia trabecular bone in cosmonauts after 6 mo of spaceflight, as measured by peripheral quantitative computed tomography (pQCT). Six months after return, many of the cosmonauts did not show full recovery of bone mineral density (BMD). Lang *et al.* (25, 26) showed that over a 4- to 6-mo period of spaceflight, BMD was lost at rates of 0.9%/mo at the spine ($P<0.001$) and 1.4–1.5%/mo at the hip ($P<0.001$). They also measured the total, trabecular, and cortical volumetric BMD (vBMD) of the proximal femur. Spinal integral vBMD was lost at a rate of 0.9%/mo ($P<0.001$), and trabecular vBMD was lost at 0.7%/mo ($P<0.05$). In summary, their results show that ISS (**Fig. 5**) crew members, on average, experienced substantial and significant loss of both trabecular and

cortical bone in the hip and somewhat smaller losses in the spine (25, 26). Later studies from ISS (25, 27–29) indicate that recovery of skeletal density after long-duration space missions may exceed 1 yr (27). It is of interest that bone loss occurred despite ~2 h of daily exercise. This suggests that microgravity-induced bone loss may have an underlying cellular mechanism causing space osteoporosis. Studies of osteoblast-like cells showed a loss of cytoskeleton integrity in spaceflight as compared to ground (30) and 1-*g* flight controls (31). Others have found cytoskeleton changes in multiple cell types in simulated microgravity and spaceflight (32–36). Finally, osteoblastic cells were shown to have altered nuclear shape and reduced anabolic gene expression of proliferating cell nuclear antigen (PCNA), transforming growth factor β (TGFβ), cyclooxygenase-2 (cox-2), cytosolic phospholipase A2 (cpla2), osteocalcin (OC), c-*myc*, and fibroblast growth factor-2 (fgf-2) when compared to normal gravity (31). Further studies will determine whether gravity itself is required for normal bone growth.

Figure 5.

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International Space Station, a U.S. National Laboratory, as seen from STS-134. Image courtesy NASA.

IMMUNOSUPPRESSION IN SPACE

On the Apollo missions, 15 of the 29 Apollo astronauts reported bacterial or viral infection during or within 1 wk of landing back on Earth (3). The relatively high incidence of infection on Apollo was thought to be correlated with the elevated cortisol levels and sympathetic activation detected in blood and urine samples from astronauts. These findings led early investigators to propose a systemic cause of infection (6, 37). Studies by Cogoli *et al.* (38, 39) demonstrated that lymphocytes have blunted activation during spaceflight, thus implicating gravity as a necessary factor in normal immune function.

Subsequent ground studies using gene arrays and quantative RT-PCR (qRT-PCR) demonstrated that gravity was needed for normal T-cell activation (40). Using a random positioning machine to simulate microgravity, we surprisingly found that the induction of 91 genes depended on the presence of gravity. Gene induction is partially regulated by transcription factors on the promoter region at the 5′ end of the gene. Promoter region analysis found that the majority of genes down-regulated in microgravity were controlled by transcription factors NFκB, CREB, ELK, AP-1 and STAT—transcription factors that lie downstream of protein kinase A (PKA) signaling (40). New preliminary data from this laboratory (41) has shown that noncoding RNA is dysregulated in T cells activated in spaceflight on ISS as compared to 1-*g* onboard controls. This new level of regulation of immune cells in spaceflight offer new opportunities to study a new technology that can help identify unique pharmaceutical targets to treat immune disease.

Although much is known about immune status immediately following spaceflight, the understanding of immunity during spaceflight is limited. The few in-flight studies that have been performed indicate that spaceflight may be specifically associated with the reactivation of latent herpes viruses and impairment of cell mediated immunity (42–48). Observations of astronaut immune status after landing have shown numerous changes in immune cell function, including altered distribution of circulating lymphocytes, altered production of cytokines, decreased function of granulocytes, and decreased activation of T cells (8). Cases of latent viral reactivation, altered viral specific immunity, and expression of early/late gene Epstein-Barr viruses have been noted in astronauts after flight (42, 45–48). Future studies of viral reactivation in spaceflight may also shed new light on viral regulation here on Earth.

Studies with isolated human T cells in flight have demonstrated a loss of expression of early activation steps (38, 49–51). Recent studies of T cell activation of “astromouse” splenocytes after 16 d of spaceflight have demonstrated a reduction in expression of the same genes as seen in astronauts after landing. Analysis of flight and ground animals for gene expression of T cell activation markers interleukin-2 (IL-2), IL-2Rα, interferon-γ (IFNγ), and tumor necrosis factor α (TNF-α) were significantly decreased 2- to 10-fold in the activated flight splenocytes as compared to ground controls. Expression of cyclophilin and VEGF was unchanged. Protein synthesis of chemokines and cytokines IL-2, IL-2Rα, IFNγ, CCL-3 and TNF-α were also decreased in the flight cell supernatants when compared to ground controls. The observed down-regulation of induced T cell activation genes combined with changes of synthesis of their proteins show that animal immune cells require gravity and that the spaceflight-induced changes in T cell function continue hours after landing (52). More important, these data correspond with previous findings of human immune function in astronauts after return to Earth and support the conclusion of a physiological dependence of the immune system on gravity. These data suggest that at least one mammalian system in two species require gravity for full function. Potential adverse clinical effects that may be related to prolonged dysfunction of the immune system and spaceflight include hypersensitivity, autoimmunity, and frequency of infectious diseases (8).

There is mounting evidence that gravity is required for normal function of bone and immune cells. Since all of life developed in a gravity environment, it is not surprising that some biological systems may be dependent on gravity force. In mathematics, when a variable is removed from an equation, many times it can be solved. It is possible that the same

is true for biological systems. Future studies of spaceflight-induced osteoporosis and immunosuppression may well yield new information and pharmaceutical targets to treat earthbound human diseases.

THE FUTURE OF INFINITY

The flight of STS-135 ended the Shuttle era. However, there are plans to use the SpaceX Falcon rocket and its capsule, Dragon, to deliver supplies and experiments to ISS in the near future. Recently, NASA gave out $92 million to Boeing to help its development of the commercial crew development (CCDev2) capsule, $80 million to the Sahara Nevada Corporation to design a shuttle-like Dream Chaser craft, and $75 million to SpaceX to make improvements in the Dragon capsule for delivery of crewmen to ISS. Considering that the U.S. government is now paying Russia $63 million per astronaut for a single trip to and from ISS, these are modest technological investments to enable the United States to have transportation to ISS.

Will the United States fund space flight investigations on ISS to yield new medical discoveries and new technology? Will progress of science and technology advance during the next century as it did in the past 60 yr? It depends on funding; in 2003 ~90% of NASA's science funding was "temporarily" cut after loss of spaceship *Columbia*; this essentially disabled all fields of space science at a time when ISS was becoming available for use. Reduced funding included cessation of student and graduate training, thereby severing the supply pipeline for the next generation of scientists. Unfortunately, that funding was never restored. Today, we are experiencing similar cuts in the National Institutes of Health budget that further limit medical research and training of new investigators.

Our future depends on today's visionaries—our writers must envision the future, our politicians must vote to fund that vision, and our schools must educate new engineers and scientists. Those engineers and scientists must work to develop new technologies and businessmen must engage the new technologies and renew our economy. Will science go to infinity and beyond by creating new jobs and securing our future prosperity? I certainly hope so.

Acknowledgments

The author is a former NASA astronaut. The title exhortation is a quote from space ranger Buzz Lightyear, in the film *Toy Story* (Pixar Animation Studios), November 22, 1995.

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